

PATENT COOPERATION TREATY

JCF
SCD

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JULIUS FISTER, III
FISH & RICHARDSON P.C.
225 FRANKLIN STREET
BOSTON, MA 02110-2804

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 16924-033WOI	Date of mailing (day/month/year) FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US04/11900	International filing date (day/month/year) 16 April 2004 (16.04.2004)
Applicant HANDYLAB, INC.	

1. ☐ The applicant is notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
- For more detailed instructions, see the notes on the accompanying sheet.
- Article 17(2)(a) of the Treaty
- For more detailed instructions, see the notes on the accompanying sheet.
- Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35
- For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Alex Noguera

Telephone No. (571) 272-3300

RECEIVED

Form PCT/ISA/220 (May 2003)

Docketed By Practice Systems
Resp to Search Report - 2-10-05

Initials: WKF

(See notes on accompanying sheet)

Docketed By Billing Secretary
Due Date: DEC 13 2004
Deadline: WJ
Initials: WJ

**FISH & RICHARDSON, P.C.
BOSTON OFFICE**

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JULIUS FISTER, III
FISH & RICHARDSON P.C.
225 FRANKLIN STREET
BOSTON, MA 02110-2804

PCT

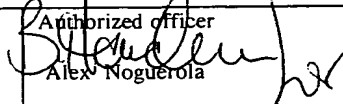
NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 10 DEC 2004	
Applicant's or agent's file reference 16924-033WOI	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US04/11900	International filing date (day/month/year) 16 April 2004 (16.04.2004)
Applicant HANDYLAB, INC.	

1. ☐ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
- Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
- When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
- Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35
- For more detailed instructions, see the notes on the accompanying sheet.**
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Reminders**
- Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.
- The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.
- Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.
- In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.
- See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer

Alex Noguerola
Telephone No. (571) 272-1300

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 16924-033WOI	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US04/11900	International filing date (<i>day/month/year</i>) 16 April 2004 (16.04.2004)	(Earliest) Priority Date (<i>day/month/year</i>) 16 April 2003 (16.04.2003)
Applicant HANDYLAB, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 1



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



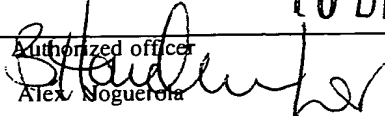
as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/11900

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : G01N 27/327 US CL : 205/777.5 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 205/777.5 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE-LOS-SANTOSALVAREZ et al. ("New scheme for electrochemical detection of DNA based on electrocatalytic oxidation of NADH," Electrochemistry Communications (March 2003), 5(3), 267-271).	54-56
X	CHO et al. ("Fabrication of a Multi-Electrode array DNA Sensor for Electrochemical Genotyping," Journal of the Korean Physical Society, vol. 41, No. 6, december 2002, pp. 1054-1057).	54-57, 61, 62, 64, 65
---		-----
Y		58, 63
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search 01 December 2004 (01.12.2004)		Date of mailing of the international search report 10 DEC 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer  Alex Noguerola Telephone No. (571) 272-1300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/11900

Continuation of B. FIELDS SEARCHED Item 3:

EAST, CAPLUS

search terms: oligonucleotides, polynucleotides, nucleic, DNA, RNA, intercalat?, electroanalytical, electrochemcial, electrode, probe, dye, methylene blue, anthracycline, daunomycin, doxorubicin, toluidine, azure, thionin

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
JULIUS FISTER, III
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225 FRANKLIN STREET
BOSTON, MA 02110-2804

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) 10 DEC 2004			
Applicant's or agent's file reference 16924-033WOI		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US04/11900	International filing date (day/month/year) 16 April 2004 (16.04.2004)	Priority date (day/month/year) 16 April 2003 (16.04.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): G01N 27/327 and US Cl.: 205/777.5			
Applicant HANDYLAB, INC.			

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

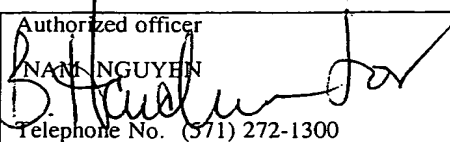
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer  NAM NGUYEN Telephone No. (571) 272-1300
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/11900

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11900

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-53 and 58-65</u>	YES
	Claims <u>54-57</u>	NO
Inventive step (IS)	Claims <u>1-53, 59, 60-62, 64, 65</u>	YES
	Claims <u>54-58 and 63</u>	NO
Industrial applicability (IA)	Claims <u>1-65</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Please See Continuation Sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US04/11900

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 56, 57, 62, 64, and 65 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because these claims are indefinite for the following reason: none of these claims have antecedent basis for "probe molecule".

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/11900

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

1) Claims 54-56 lack novelty under PCT Article 33(2) as being anticipated by de-los-SantosAlvarez et al. ("New scheme for electrochemical detection of DNA based on electrocatalytic oxidation of NADH," *Electrochemistry Communications* (March 2003), 5(3), 267-271).

See the abstract; 2.2 Apparatus and procedures; and Figures 1-3.

2) Claims 54-57 and 61, 62, 64, and 65 lack novelty under PCT Article 33(2) as being anticipated by Cho et al. ("Fabrication of a Multi-Electrode Array DNA Sensor for Electrochemical Genotyping," *Journal of the Korean Physical Society*, Vol. 41, No. 6, December 2002, pp. 1054-1057).

See the abstract; 2. DNA Immobilization, Hybridization, and Washing;

3. Intercalation and Electrochemical Measurement of Indicator; and Figure 3.

3) Claims 58 and 63 lack an inventive step under PCT Article 33(3) as being obvious over Cho et al. ("Fabrication of a Multi-Electrode Array DNA Sensor for Electrochemical Genotyping," *Journal of the Korean Physical Society*, Vol. 41, No. 6, December 2002, pp. 1054-1057) ("Cho"). Claim 54, from which claim 58 depends, and claim 61, from which claim 63 depends, have been addressed above. Although Cho only discloses polynucleotide sequences having a length greater than 8 bases, the length of the bases in the probe will just depend on the target sequence. That is, on how many bases are needed for accurately selecting the target sequence.

4) Claims 1-53 and 59 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the electrochemical methods required by independent claims 1, 14, 21, 27, 46, 54, and 61.

In particular, the novelty of

* Claim 1 is that it requires "obtaining a second electrochemical signal comprising a portion arising from a second amount of probe molecule not intercalated with the target polynucleotide";

* Claim 14 is that it requires "obtaining a second electrochemical signal from a second amount of probe molecule";

* Claim 21 is that it requires "obtaining a second electrochemical signal from a second amount of the probe molecule immobilized with respect to the electrode";

* Claim 27 is that it requires "using the electrode to obtain a second electrochemical signal, the second electrochemical signal indicative of a second amount of probe molecule and arising from the polynucleotide-free electrochemically active moiety of the probe molecule"; and

* Claim 46 is that it requires "obtaining a second electrochemical signal from the probe molecule".

In Makino et al. (EP 1065278 A2) the signal subsequent to the first electrochemical signal (which is the "background

**WRITTEN OPINION OF THE
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International application No.
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

electric current") does not comprise a portion arising from an amount of probe molecule not intercalated with the target polynucleotide. See claim 2 and Figure 2.

5) Claims 1-65 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry. The methods can be used to detect polynucleotides.